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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,180	03/18/2004	Michele Cargill	CL1511ORD	6182

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,180	CARGILL ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,29-36,39-45,56 and 59-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 29-36, 39-45, 56, and 59-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 29-36, 39-45, 56, and 59-73 are pending and examined on the merits.

1. Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 10/30/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Withdrawn Claim Objections

3. The objection to claims 29, 39, 49, and 59 as recited in the previous Office Action is **WITHDRAWN** in light of the amendments to claims 29, 39, and 59, and the cancellation of claim 49.

Withdrawn Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

4. The rejection of claims 29, 32, 39, and 59 under 35 U.S.C. 112 2nd ¶, as being indefinite, as presented in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

5. Claims 36, 39-45, 56, and 59-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36, 39-45, 56, and 59-65 are unclear over the recitation of the phrase 'wherein the presence of CC at position 101', as recited in claims 36 and 56. The claims are drawn to detection of a single nucleotide polymorphism (SNP) at position 101 of SEQ ID NO: 5502, thus it is unclear what specific content in the recited 'CC' dinucleotide is required to be detected at the indicated position, and what particular single nucleotide is required to have the recited functionality of indicating an increased risk for RF+ RA.

Maintained Claim Rejections - 35 USC § 112 1st - Written Description

6. Claims 1 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov); also MPEP 2163.

The rejected claims are drawn to methods comprising detecting a single nucleotide polymorphism (SNP) at position 101 o SEQ ID NO: 5502 or its complement, wherein the presence of the SNP is correlated with an altered risk for RF+ RA. The claims are thus broadly drawn to methods comprising the detection of a variety of nucleic acids, including any SNP variant at position 101 of SEQ ID NO: 5502 that is associated with an altered risk for RA.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the detection of a variety nucleic acid sequences. The claims are drawn to a plurality of nucleic acids that encompass a genus of SNP variants in which position 101 SEQ ID NO: 5502 may have any nucleotide content (A or G or C or T, as well as a deletion or insertion of any nucleotide (specification page 6 lines 12-19). Thus the claims encompass at least the detection of any of 9 different nucleic acids (i.e. any of four substitutions at position 101, or any of four insertions at position 101, or a deletion of position 101) wherein the nucleic acid sequence is correlated with any altered risk for RA. Nucleic acid members of this genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID NO: 5502 as well as the identical sequence in SEQ ID NO: 1658 wherein the nucleotide at position 101 is indicated to be polymorphic and can be either an A or a G,

and provides an analysis indicating that the presence of an A is correlated with an decreased risk of developing RF+ RA. The specification does not provide any other polymorphic positions of SEQ ID NO: 5502 that would result in any other alteration in the sequence disclosed as SEQ ID NO: 5502 that is correlated with any altered risk for any RA. With specific regard to claims 36, 38-45, 56, and 59-73, while the claims specify a nucleotide content at position 101 of SEQ ID NO: 5502 (e.g. either a C or a T), it is noted that the claims do not provide any language regarding the complement of the required SEQ ID NO, and the specification does not provide for identification of a C or T at position 101 of SEQ ID NO: 5502 as required by the claims (the specification indicates that position 101 of SEQ ID NO: 5502 may be either an A or a G).

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not provide any characteristics that would allow the identification of the broadly claimed SNPs in SEQ ID NO: 5502 other than the A/G at position 101 (or a T/C at position 101 of the complement of SEQ ID NO: 5502) which would allow for the identification of an individual who has an altered risk for developing RF+ RA. Neither the instant specification nor the prior art provide guidance as to how one would a priori identify any of the broadly claimed SNP at position 101 of SEQ ID NO: 5502 that is indicative of a particular alteration in the risk of developing RA.

Applicants' attention is directed to the decision in In re Shokal, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, the specific information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for identification of an individual with an altered risk for developing RA by determining the presence of a SNP in SEQ ID NO: 5502 other than methods using the A/G SNP at position 101 of SEQ ID NO: 5502, or the complement thereof.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ for lack of adequate written description. Applicants argue (p.8 of Remarks) that the SNP that is claims is indicated by the designation 'R' at position 101 of SEQ ID NO: 5502, where 'R' symbolizes either A or G content at the position. This argument in light of the amendments to the claims has been considered but is not found to be persuasive. As

detailed in the rejection, the specification indeed provides specifically for either A/G content at position 101 of SEQ ID NO: 5502 (or C/T content at position 101 of the complement of SEQ ID NO: 5502) as associated with altered risk of RA, but this disclosure of particular nucleotide content is not a limiting definition of a SNP. As noted in the rejection, page 6 of the specification teaches the breadth of nucleotide content encompassed by the term 'SNP', where the presence of any nucleotide, or the insertion or deletion of any nucleotide is included. The claims still encompass methods comprising the detection of sequences not described in the specification as being indicative of altered risk of RA; the rejected claims encompass the detection of any nucleotide content at position 101 of SEQ ID NO: 5502 (e.g. claims 1 and 29-35).

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement

7. Claims 1, 29-36, 39-45, 56, and 59-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for,

> A method for identifying a human individual who has a decreased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids; and
> detecting the nucleotide content at position 101 of SEQ ID NO: 5502 or the complement of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide A at position 101 of SEQ ID NO: 5502, or detecting the nucleotide T at position 101 of the complement of SEQ ID NO: 5502, identifies the individual as having a decreased risk for developing RF+ RA.

does not reasonably provide enablement for methods comprising the detection of the presence of a G at position 101 of SEQ ID NO: 5502 (other than detection of G G homozygosity of position 101 of both alleles of SEQ ID NO: 5502 being indicative of an increased risk of RA), or identification methods comprising correlating any other nucleotide content at any other position in SEQ ID NO: 5502 with any form or RA other than RF+ RA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for identifying an individual who has an altered risk for developing RA.

The claims encompass detecting any SNP broadly claimed as 'a SNP at position 101 of SEQ ID NO: 5502'.

The claims broadly encompass methods in which detection of a SNP is correlated with any altered risk (i.e. increased risk or decreased risk) of RF+ RA.

The claims specifically encompass the detection of CC at position 101 of SEQ ID NO: 5502 (claims 36, 39-45, 56, and 59-65) and T at position 101 of SEQ ID NO: 5502 (claims 56, and 59-73).

The nature of the invention requires knowledge of an association between broadly claimed nucleic acid content and altered risk of having RA.

Direction provided by the specification and working example

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.28 – p.8 ln.4).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 5502, which may be either an A or a G, and is also identified as hCV163035 and known in the art as rs2276864. The specification teaches that the frequency of the particular allele was analyzed in two (p.120 ln.26 – p.121 ln.11) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that the Replication set was analyzed in totality (i.e. an 'all' stratum) after stratification of the subjects into an RF+ stratum (p.12; p.121 ln.28).

The specification teaches the specific association of the A allele (i.e. an A nucleotide a position 101 of SEQ ID NO: 5502) with a decreased risk of RA as the A allele is found at a significantly higher frequency in control samples in the Discovery Set and the Replication Set (Table 6;). It is noted that Table 6 designates the 'T' allele as associated with the decreased risk of RA, and the specification indicates that nucleotide content may be described as the reverse of the nucleotide content at the position (e.g. p.20, lns.25-30), thus the T allele of the reverse complement of SEQ ID NO: 5502 is the

A allele of SEQ ID NO: 5502. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+ (p.120 ln.29). While the instant specification provides that the A allele is indicative of a decreased risk for RA in the Replication Set in the 'All' Stratum, the specification provides no indication as to how many of the cases in the Replication Set were either RF+ or RF- (i.e. while the specification indicates that the Replication Set had 840 patients, it is not known if there were enough of both RF+ and RF- individuals to make data regarding the 'All' stratum significant for both RF+ and RF-). Thus it is not possible to determine from the data of Table 6 indicating a significant relationship between the A allele of SEQ ID NO: 5502 and decreased risk of RA is in fact significant within the RF- population of cases under analysis. Thus while the data of specification teaches an association of the A allele with decreased risk of RF+ RA, it is not clear from the specification if the A allele is specifically associated in the same way, or in a significant fashion, with RF- RA.

Because the claims do not clearly specify the detection of homozygous G content at position 101 of SEQ ID NO: 5502 in the determination of increased risk of RF+ RA (it is noted that independent claims 36 and 56 recite the unclear phrase 'the presence of CC at position 101'), where determination of heterozygosity at the position (i.e. and individual with one of each allele) would be detection of both alleles, it is relevant to point out that the data presented in the instant specification (i.e. Table 6) indicates only that the presence of a T allele (which is an A allele in SEQ ID NO: 5502) is indicative of a decreased risk of RF+ RA. The data does not stratify the data based on genotype

(i.e. CC vs CT vs TT), and thus appears to present only that detection of a T allele (i.e. either in a CT or TT genotype) is indicative of decreased risk of RF+ RA as compared to a CC individual, and does not provide a comparison of the relative risk of RF+ RA in a CT versus a CC individual. Thus while it is possible for the data to support that the presence of an A at position 101 of SEQ ID NO: 5502 is indicative of decreased risk of RF+ RA (because presence of either an AA or AG genotype would have a decreased risk), the data would not support making a determination based only on the presence of a single G allele (because it would not be known if the individual has a GG (increased risk) genotype or an AG (decreased risk) genotype).

The instant specification provides only the association analysis of either an A or a G at position 101 of SEQ ID NO: 5502 (as consonant with the Election), and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 5502.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach an association between any polymorphism at position 101 in SEQ ID NO: 5502 and altered risk for developing RA. And because the claims encompass the detection of a variety of polymorphic nucleotide content at

position 101 of SEQ ID NO: 5502, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Quantity of experimentation required

A large amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would include examining an association of any nucleotide content at position 101 of SEQ ID NO: 5502 with the risk of RF+ RA. This would involve large case:control studies in multiple human populations, and the analysis of different polymorphic variants of SEQ ID NO: 5502, where the specification provides only for the detection of either A or G at position 101 of SEQ ID NO: 5502. Even if such an analysis were to be performed, there is no assurance that one would find any significant associations beyond those specifically taught in the particular example of the instant specification.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement. Applicants have argued (p.8-9 of Remarks) that the claims have been amended to specifically point out the number of alleles that are required for either increased risk or decreased risk association. This argument is not found to be persuasive, as the recitation of the phrase 'the presence of CC at position 101 of SEQ ID NO: 5502' (i.e. as recited in independent claims 36 and 56) is not a required limitation of detecting the presence of G at position 101 of both alleles of SEQ ID NO: 5502 (where the specification supports the identification of G at position 101 of SEQ ID NO: 5502, or the identification of C at position 101 of the complement of SEQ ID NO: 5502).

It is noted that with regard to the rejection of claims, the claims specifically require that, for example, the presence of T at position 101 of SEQ ID NO: 5502 is indicative of decrease risk of developing RA, where the specification indicates that position 101 of SEQ ID NO: 5502 may be either an A or a G. While the claims recite the phrase 'or its complement thereof' (e.g. claim 66 recites 'wherein the presence of T at position 101 of SEQ ID NO: 5502 or its complement thereof'), this recitation does not serve to clearly limit the subject matter of the claims to the subject matter enabled by the specification. For example, claim 66 encompass the detection of T at position 101 of SEQ ID NO: 5502, where such detection is not enabled by the specification. If Applicants wish to include language specifying analysis of a sequence complementary to the disclosed sequence, language such as:

detecting the nucleotide A at position 101 of SEQ ID NO: 5502, or detecting the nucleotide T at position 101 of the complement of SEQ ID NO: 5502

may more clearly specify the subject matter enabled by the instant specification. As detailed in the rejection, the data presented in the specification (Table 6) supports only the identification of an A at position 101 of SEQ ID NO: 5502 (i.e. identification of either an AA or AG genotype) as indicative of a decreased risk of RF+ RA); the data does not support the detection of a single G (or C in the complement) allele, or dinucleotide GG (or CC in the complement) allele, as indicative of an increased risk of RF+ RA.

The rejection as set forth is **MAINTAINED**.

Conclusion

8. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

J. Goldberg

JEANINE A. GOLDBERG
PRIMARY EXAMINER
1/28/08